# Soft-tissue Sarcomas

## *Diagnosis and Management*


**Jon Trent, MD, PhD**

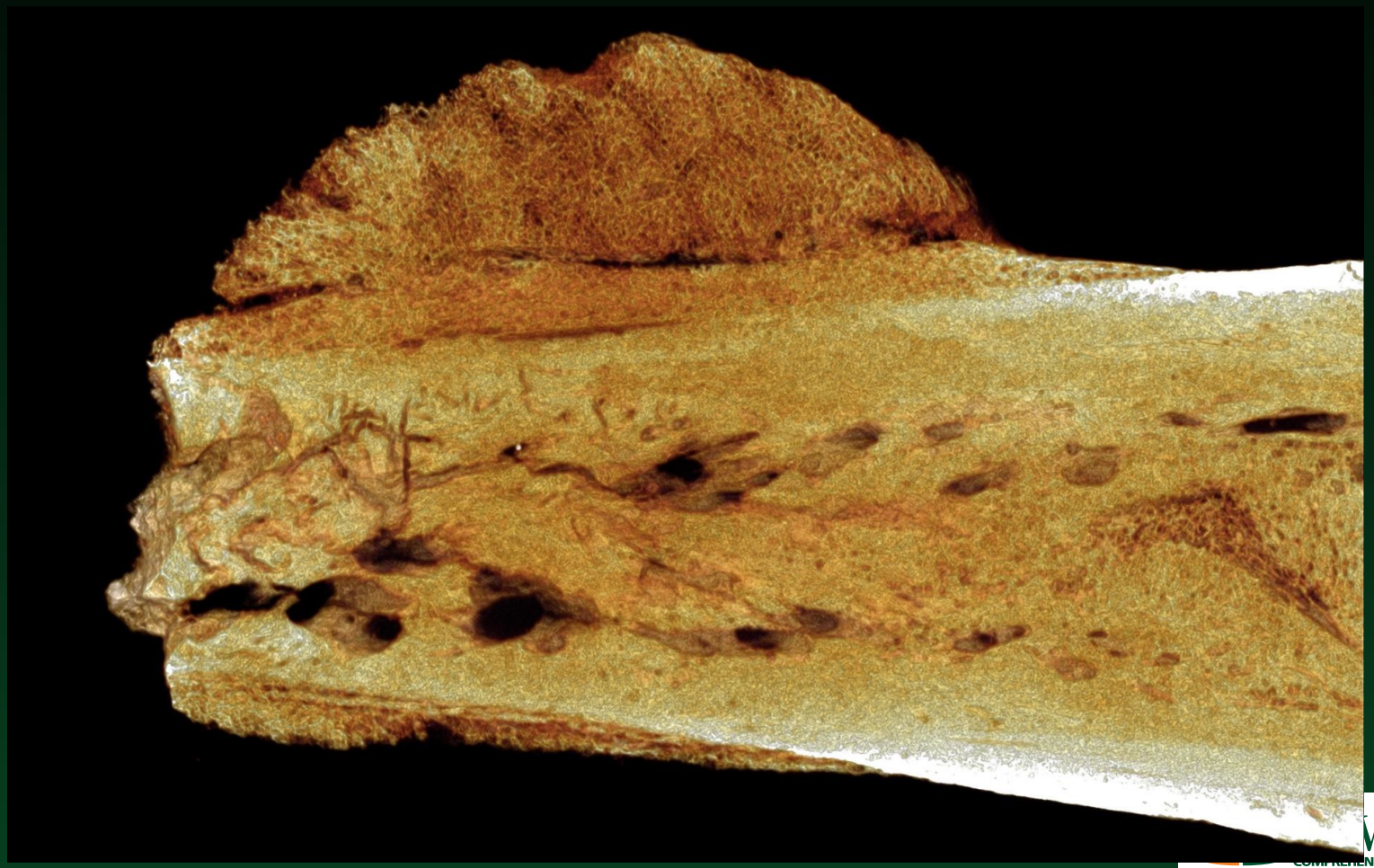
**Professor of Medicine**
**Director, Bone and Soft-tissue Sarcoma**
**Associate Director, Clinical Research**
**The University of Miami,**
**Sylvester Comprehensive Cancer Center**
**jtrent@med.miami.edu**
**@JTrentMDPhD**


SYLVESTER
COMPREHENSIVE CANCER CENTER

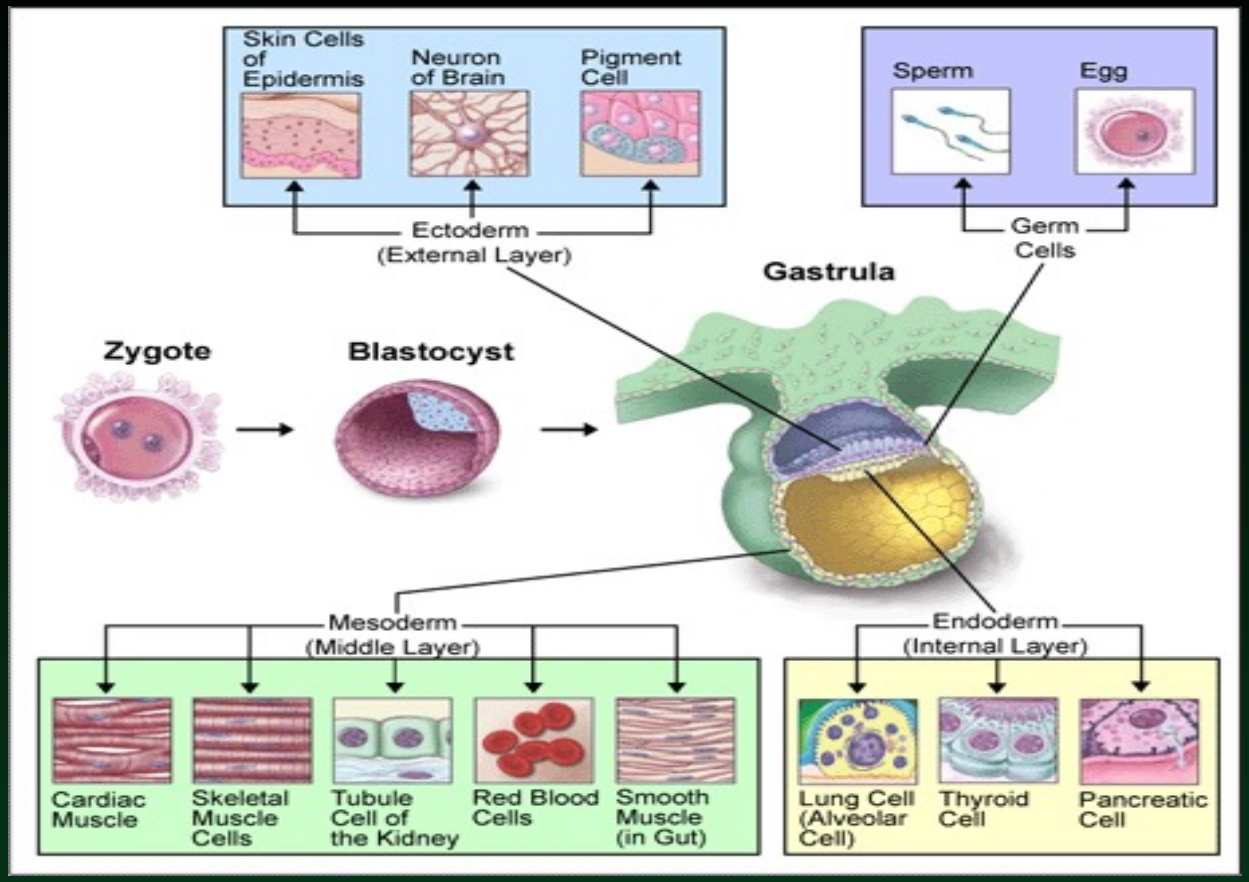
UNIVERSITY OF MIAMI HEALTH SYSTEM

# First Sarcoma (Osteosarcoma)

## ~1.7 million years ago



Randolph-Quinney, et al. SAJS, 2016




*http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html*

# Molecular Sarcomagenesis

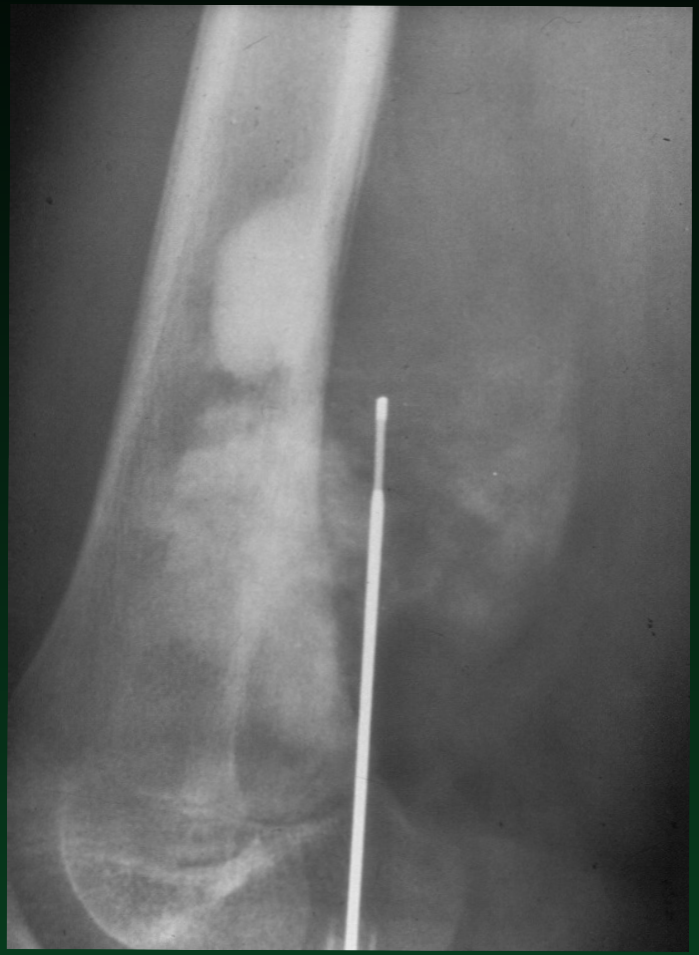
- **Point mutations**
  - GIST: *KIT, PDGFR, RAF*
  - Myxoid Liposarcoma: PTEN, PI3K, AKT
- **Gene Amplification**
  - Dediff Liposarcoma: MDM-2, CDK4
  - Neuroblastoma: *n-myc*
- **Gene Deletion**
  - Osteosarcoma: *p53*
  - Retinoblastoma*: RB1*
- **Translocation**
  - Ewing's Sarcoma: *EWS-FLI1*
  - Dermatofibrosarcoma*: Col1A-PDGFB*
- **Protein Overexpression**
  - Desmoid Tumor: ER

# Anatomic Distribution

| Location | Percentage |
|---|---|
| Head and neck | 10 |
| Thorax | 10 |
| Abdomen | 11 |
| Pelvis | 8 |
| Upper Extremity | 16 |
| Lower Extremity | 29 |
| Unknown | 17 |

# Diagnosis

# Tru-Cut (Core) Biopsy



SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Discrepancies Between Primary Diagnosis and Second Opinion in Patients With Sarcoma

| Study | Full Agreement With Second Opinion, % | Minor Discrepancy With Partial Discordance, % | Major Discrepancy With Complete Discordance, % |
|---|---|---|---|
| Lurkin et al[1] N = 366 | 54 | 27 | 19 |
| Arbiser et al[2] N = 266 | 68 | 7 | 25 |

1. Lurkin et al. *BMC Cancer* 2010;10:150.
2. Arbiser et al. *Am J Clin Pathol.* 2001;116:473-476.

# Current Classification of Sarcomas

- **Vascular STSs**
  - Angiosarcoma
  - Hemangiosarcoma
  - Lymphangiosarcoma
  - Hemangioendothelioma
  - Hemangiopericytoma
  - Kaposi's Sarcoma
- **Neural STSs**
  - Malignant Peripheral Nerve Sheath Tumor
  - Malignant Paraganglioma
  - Neuroblastoma, Neuroepithelioma
  - Granular Cell Tumor
- **Adipose STSs**
  - ALT
  - Myxoid/Round cell Liposarcoma
  - Dedifferentiated Liposarcoma
- **Pleomorphic STSs**
  - Lipo, MFH
- **Neuromuscular STS**
  - GI Stromal Tumor
- **Unclassified**

N=175

- **Smooth Muscle STSs**
  - GI, GU, Cutaneous, Vascular
- **Skeletal Muscle STSs**
  - ARMS, ERMS, Pleomorphic RMS
- **Fibrous STSs**
  - Fibrosarcoma
  - Fibromyxoid Sarcomas
  - Desmoid Tumor
  - Dermatofibrosarcoma
  - Inflammatory myofibroblastic tumor
- **Unknown Tissue**
  - Synovial Sarcoma
  - ASPS
  - Epithelioid Sarcoma
- **Bone Sarcomas**
  - Osteosarcoma (+ variants)
  - Chondrosarcoma (+ variants)
  - Giant Cell Tumor of Bone
  - Ewing's Sarcoma Family of Tumors
- **Extraskeletal Bone Sarcomas**
  - Osteosarcoma
  - Ewing's Sarcoma C

# Soft Tissue Sarcomas

## *Sites of Metastases*

- **Lung: most; but rare with GIST, desmoid tumor, DFSP**
- **Liver: GIST, Leiomyosarcoma, Angiosarcoma**
- **Fat: Myxoid liposarcoma**
- **Brain: Angiosarcoma, ASPS**
- **Bone: PNET, Angiosarcoma, Hemangioendothelioma**
- **Lymph Nodes: Epithelioid Sarcoma, SDH-deficient GIST, Clear cell sarcoma, Angiosarcoma**

# Management

## Metastatic Soft-tissue Sarcoma

# Soft-tissue Sarcomas

## *Active Systemic Agents*

- Adriamycin
- Ifosfamide
- High-dose ifosfamide
- DTIC, Temozolomide
- Gemcitabine
- Docetaxel, Paclitaxel
- Irinotecan
- Vincristine
- VP-16
- Trabectedin
- Imatinib, sunitinib, regorafenib, ripretinib, avapritinib
- Pazopanib
- Eribulin
- Tazemetostat
- Denosumab
- mTOR inhibitors
- Nirogacestat

# Soft-tissue Sarcomas

*Sensitivity to Systemic Agents*

- **Very sensitive histologies :**
  - Ewing's/PNET, Rhabdomyosarcoma, DSRCT, GIST, DFSP, Angiosarcoma, Myxoid/round cell sarcoma
  - Desmoid Tumors, Solitary Fibrous Tumor
- **Intermediately sensitive histologies :**
  - fibrosarcoma, MPNST, solitary fibrous tumor, Extraskeletal myxoid chondrosarcoma, synovial, leiomyosarcoma, Alveolar Soft-parts Sarcoma, PEComa
- **Minimally sensitive histologies:**
  - Epithelioid sarcoma, dediff liposarcoma,
- **Resistant histologies:**
  - Clear-cell sarcoma, GI leiomyosarcoma, Epithelioid Hemangioendothelioma

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Advanced Soft-tissue Sarcomas

*Single Agent Doxorubicin Efficacy*

| Doxorbucin Dose | Objective Response Rate |
|---|---|
| 45 mg/m2 | 18 % |
| 60 mg/m2 | 20 % |
| 75 mg/m2 | 37 % |
| Various | 5-25% |

O'Bryan et al, *Cancer* 1977
Judson et al, Lancet Onc 2014

*Single Agent Ifosfamide Efficacy*

| Ifosfamide Dose (Gm/m2) | Objective Response Rate |
|---|---|
| 6 | 10 % |
| 8 | 17 % |
| 10 | 21 % |
| 14 (infusion) | 29 % |
| 14 (bolus) | 57 % |

Patel JCO 1997

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Doxorubicin Plus Ifosfamide (AI) Prospective Trials for STS

| Dose | No. of Pts. | RR% |
|---|---|---|
| AI (50/5000 mg/m$^2$) | 258 | 25 |
| AI (60/7500 mg/m$^2$) | 88 | 34 |
| AI (75/5000 mg/m$^2$) | 104 | 45 |
| AI (75-90/10,000 mg/m$^2$) | 79 | 65 |


Santoro *et al. JCO*. 13:1537-1545, 1995.

Edmonson *et al. JCO.* 11:1269, 1993

Steward *et al. JCO.* 11:15-21, 1993.

Patel et al, 2000

# Doxorubicin + Ifosfamide is Superior to Doxorubicin Alone

## *(intention to treat analysis)*

OS

PFS

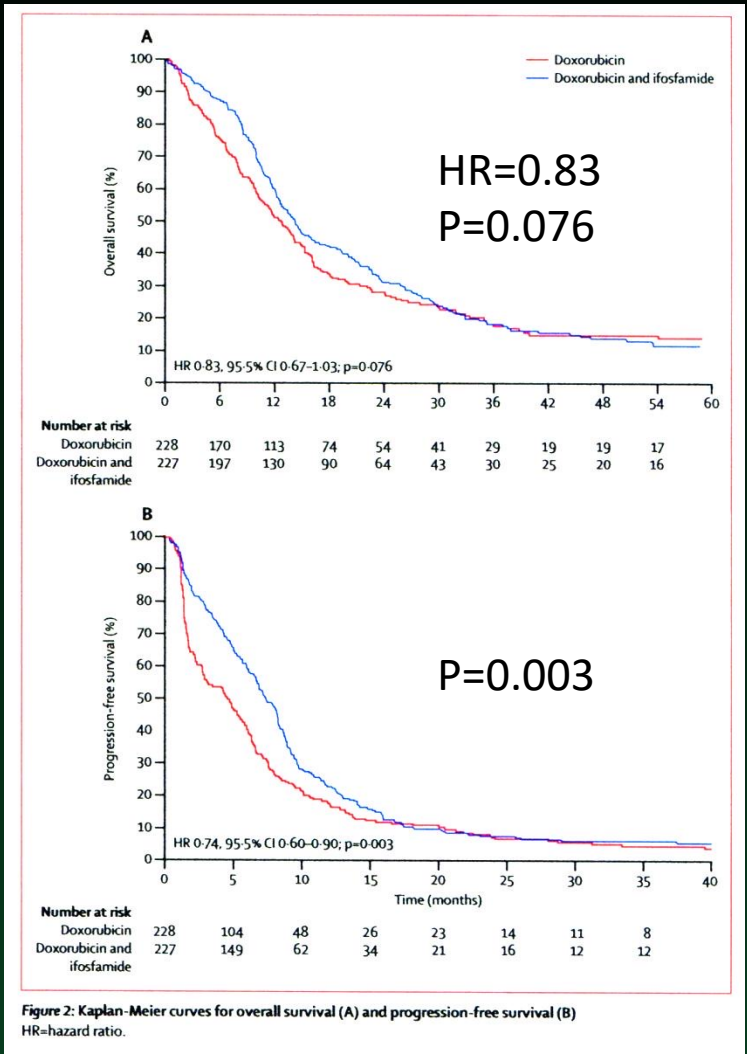



*Figure 2:* Kaplan-Meier curves for overall survival (A) and progression-free survival (B)
HR=hazard ratio.

Overall response rate:
Doxorubicin: **13.6%**
Doxorubicin + ifosfamide: **26.5%**

Median PFS
Doxorubicin: **4.6 mths**
Doxorubicin + ifosfamide: **7.4 mths**

Median overall survival:
Doxorubicin: 12.8 mths
Doxorubicin + ifosfamide: 14.3 mths
**1.5 month increase in median OS**

1 Year Overall Survival
Doxorubicin: **51%**
Doxorubicin + ifosfamide: **60%**

*Judson et al Lancet Oncol 2014;15(14):415-23*

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# RECIST "Best response" data
## (n=116 evaluable)

| | Gem (n=47) | Gem / Doc (n=69) | TOTAL |
|---|---|---|---|
| **PR/CR** | 4 (9%) | 13 (19%) | 17 (15%) |
| **SD** | 24 (51%) | 37 (54%) | 61 (53%) |
| **SD: 24 week** | 9 (19%) | 12 (17%) | 21 (18%) |
| **PD** | 19 (40%) | 19 (27%) | 38 (32%) |

# Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial

*Lancet Oncol* 2017; 18: 1397–410

*Beatrice Seddon, Sandra J Strauss, Jeremy Whelan, Michael Leahy, Penella J Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Charlotte Benson, Nasim Ali, Maria Marples, Gareth J Veal, David Jamieson, Katja Küver, Roberto Tirabosco, Sharon Forsyth, Stephen Nash, Hakim-Moulay Dehbi, Sandy Beare*

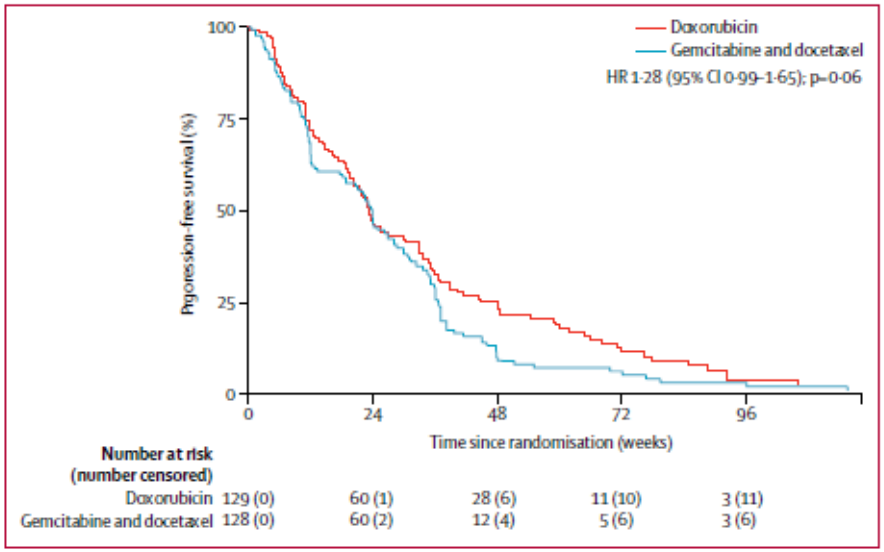



*Figure 2*: Progression-free survival
HR=hazard ratio.

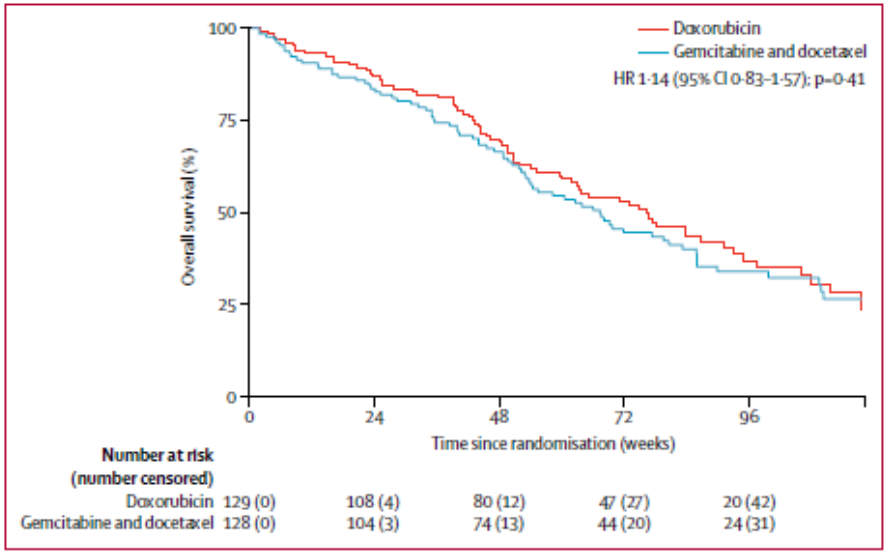
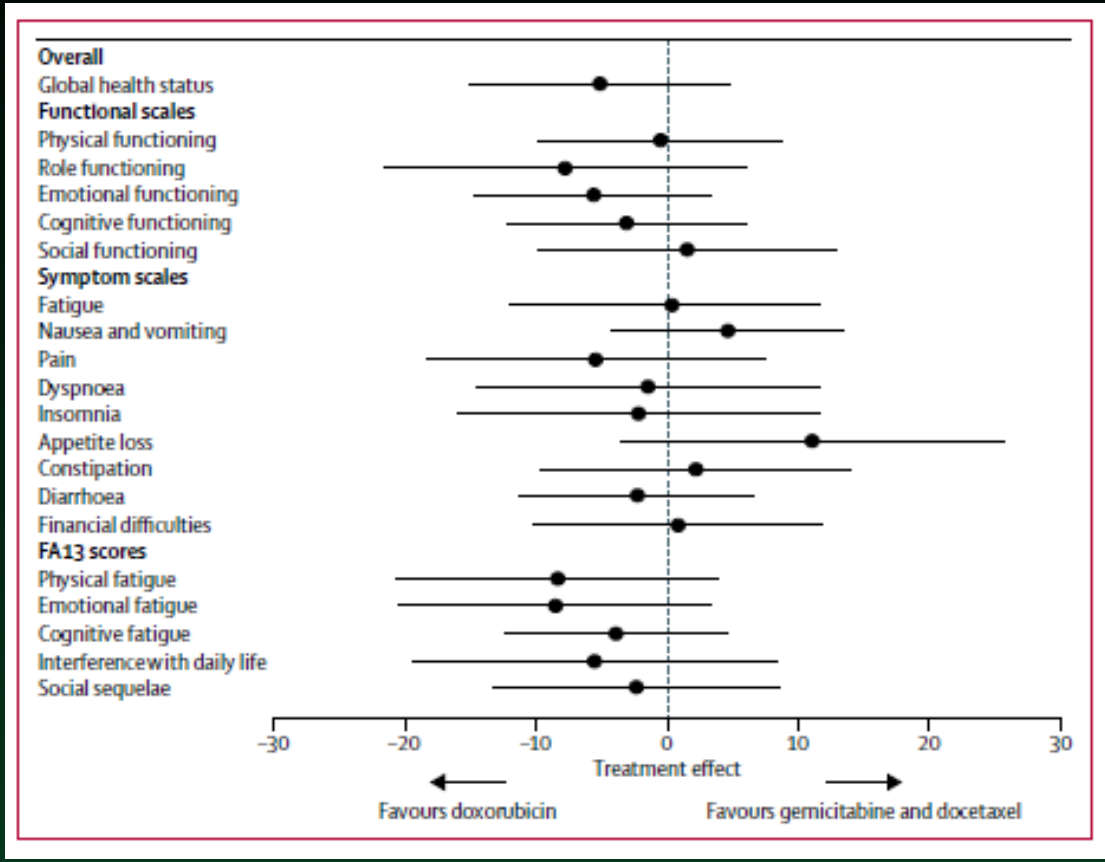



*Figure 3*: Overall survival
HR=hazard ratio.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Toxicity
## *doxorubicin vs Gem/doce*

- **The combination (G+D) should not be considered as routine, while doxorubicin should remain standard of care, in the first line setting for Soft Tissue Sarcoma (regardless of subtype)**




SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Soft Tissue Sarcomas

## *Temozolomide Chemotherapy*

- Two-arm phase 2 study, GISTs vs. others
- 85 mg/m$^2$ PO daily
- 0/17 responses in GISTs
- **4/39 PRs (9%)** in other histologies
  - **2/13 (15%) leiomyosarcomas** (uterus, RP, vascular)
- Well tolerated

*Trent et al. Cancer 19:3483-*

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Pazopanib vs Placebo in PALETTE
## Efficacy

- Pazopanib was associated with significantly longer PFS (4.6 months vs 1.6 months; HR = 0.31, 95% CI 0.24–0.40; *P*<0.001) (figure A).
- Differences in OS between pazopanib and placebo were not significant (12.5 months vs 10.7 months; HR = 0.86, 95% CI 0.67–1.11; *P*=0.2514) (figure B).

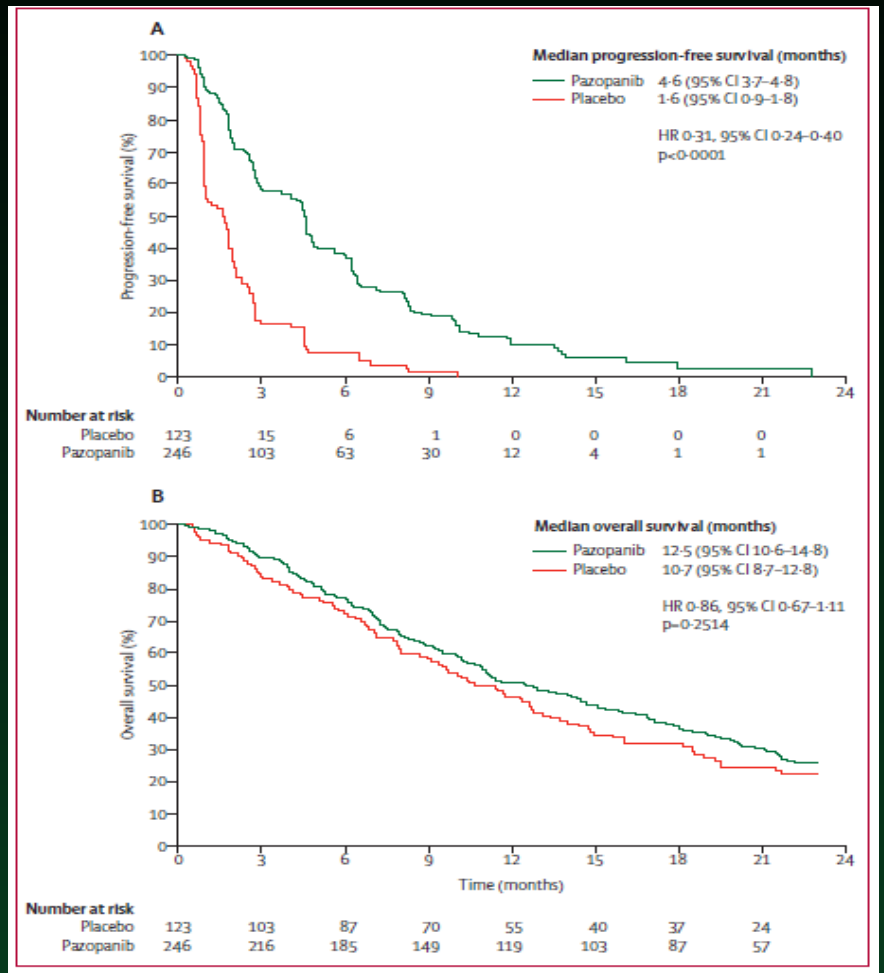
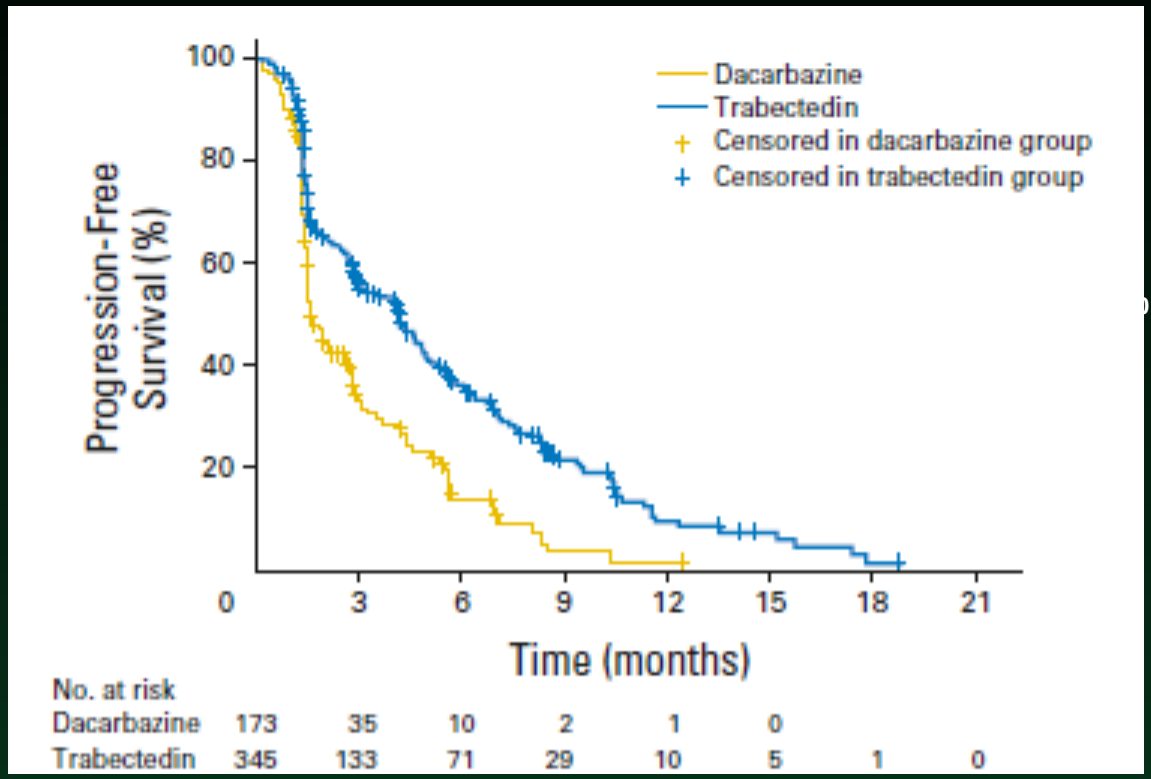



***Figure 2:*** **Kaplan-Meier curves for survival**
Progression-free (A) and overall (B) survival. 106 patients died or had disease progression in the placebo group, 168 in the pazopanib group (cutoff Nov 22, 2010). 95 patients died in the placebo group, 185 in the pazopanib group (cutoff Oct 24, 2011).

HR = hazard ratio; CI = confidence interval.

van der Graff WT et al. *Lancet*. 2012;379:1879-1886.

# Trabectedin vs Dacarbazine: PFS
## *Liposarcoma and Leiomyosarcoma*




01.

- **PFRs at 3 and 6 months were 56% and 37% in the trabectedin arm versus 34% and 14% in the dacarbazine arm.**

**Demetri GD et al. *J Clin Oncol.* 2016;34:786-793.**

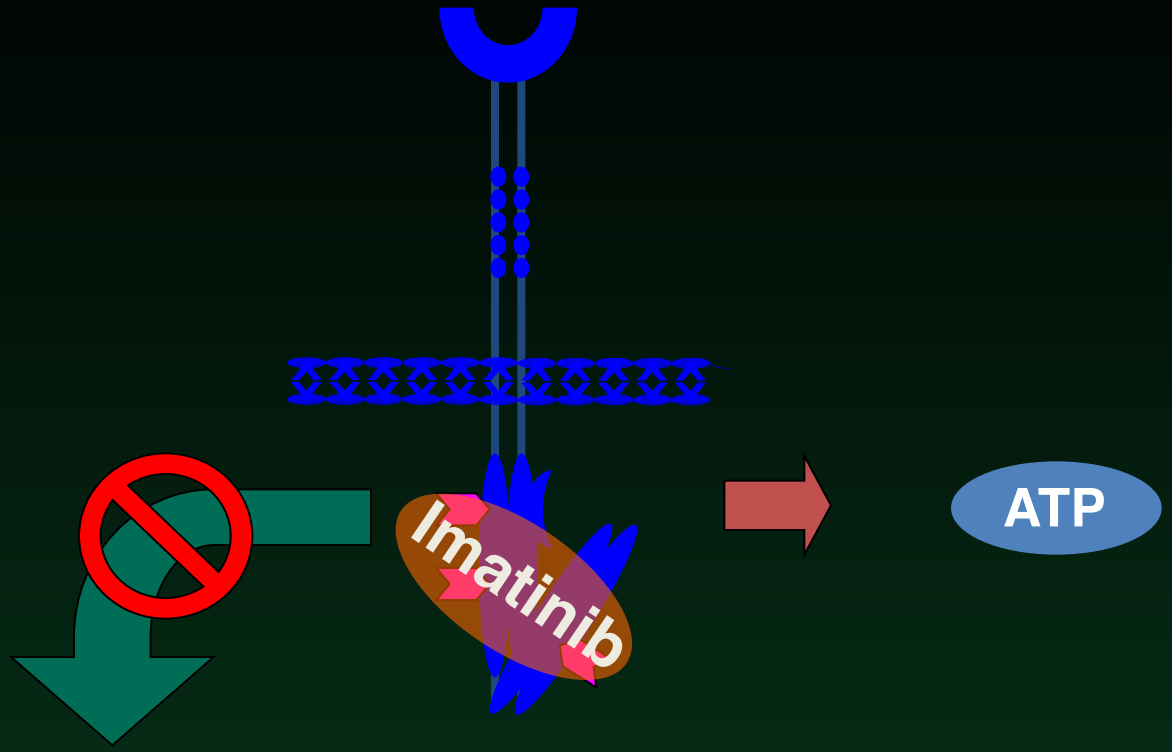
# Precision Oncology

SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- High frequency of metastatic disease
- Gene mutations drive phenotype and therapy
- Metastatic disease treated with tyrosine kinase inhibitors (TKIs)
  - **Imatinib** (PFS = 24 months)
  - **Sunitinib** (PFS = 6 months)
  - **Regorafenib** (PFS = 5 months)
  - **Ripretinib** (PFS = 6.3 months)
  - **Avapritinib (PFS = 3.7 months)**
  - **Avapritinib PDGFR (PFS = NR)**

# Kit Receptor Phenotype




Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

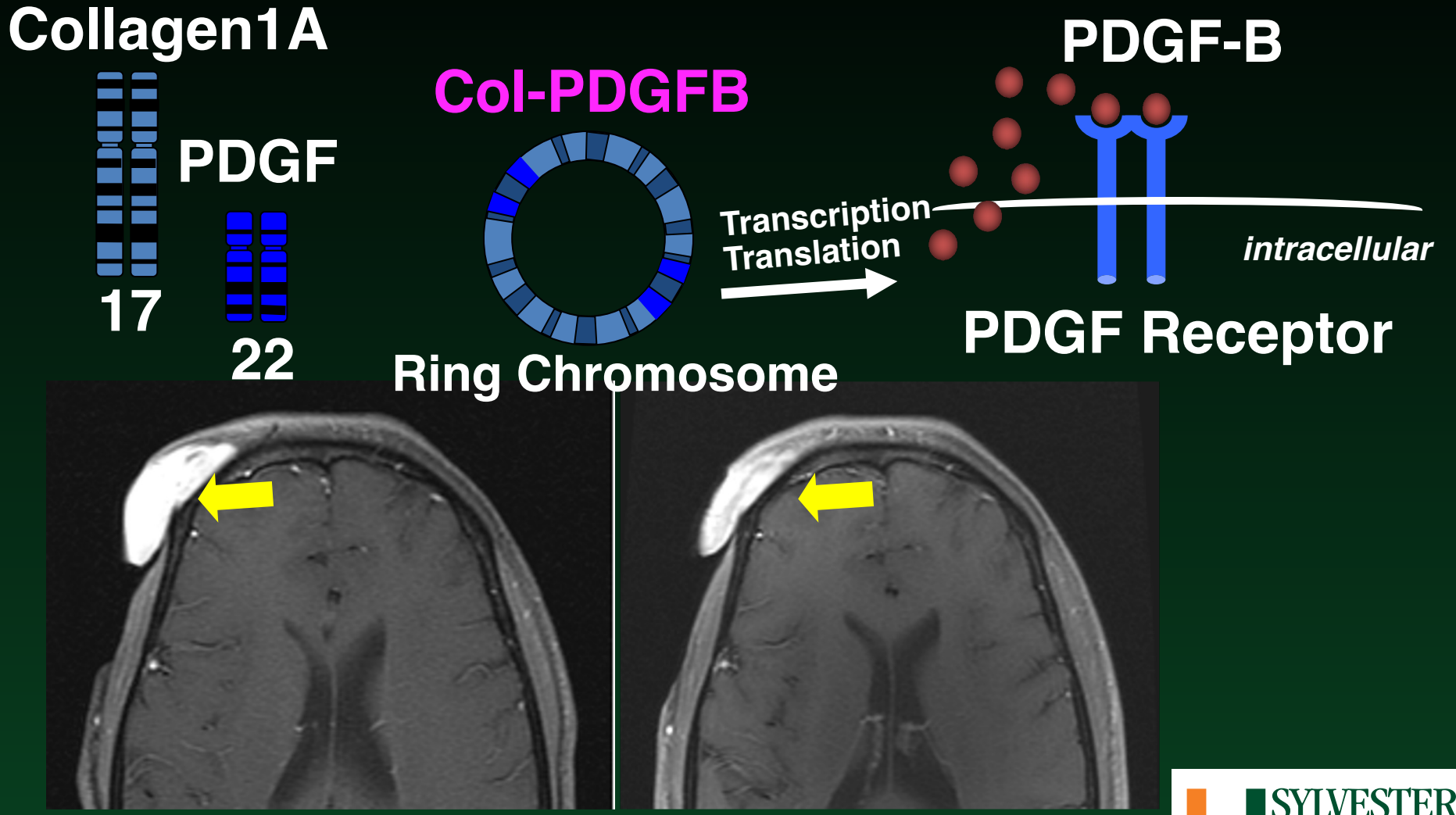
# GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: avapritinib
- SDH deficiency: Sunitinib or Regorafenib (TMZ trial)
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – Larotrectenib NTRK inhibitor
- KIT resistance mutations
  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Regorafenib or Ripretinib

Jon Trent, MD, PhD

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# PDGFR Inhibitors in Dermatofibrosarcoma





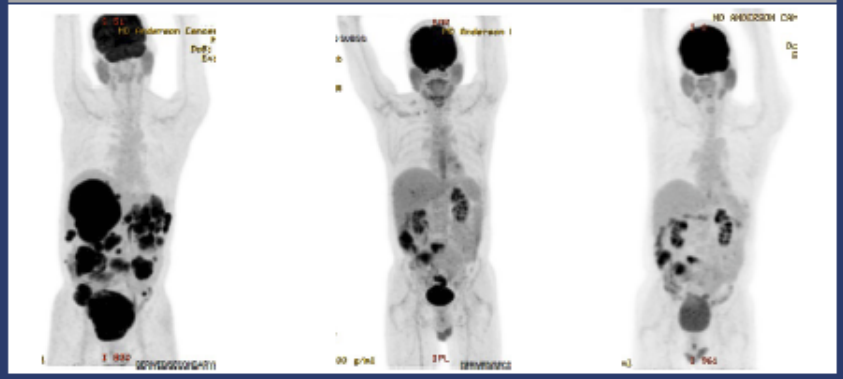

*Tibes, Trent, Kurzrock. Ann Rev Pharmacol Toxicol. 45:357-84*

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Sarcoma With TRK Fusion

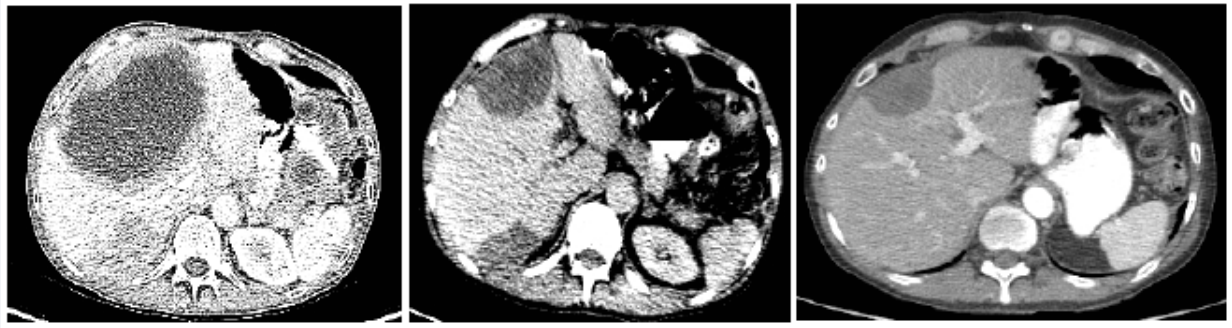
**Patient #2:**
**ETV6-NTRK3 fusion**

PET



Study baseline | Study cycle 3 day 1 | Study cycle 9 day 1

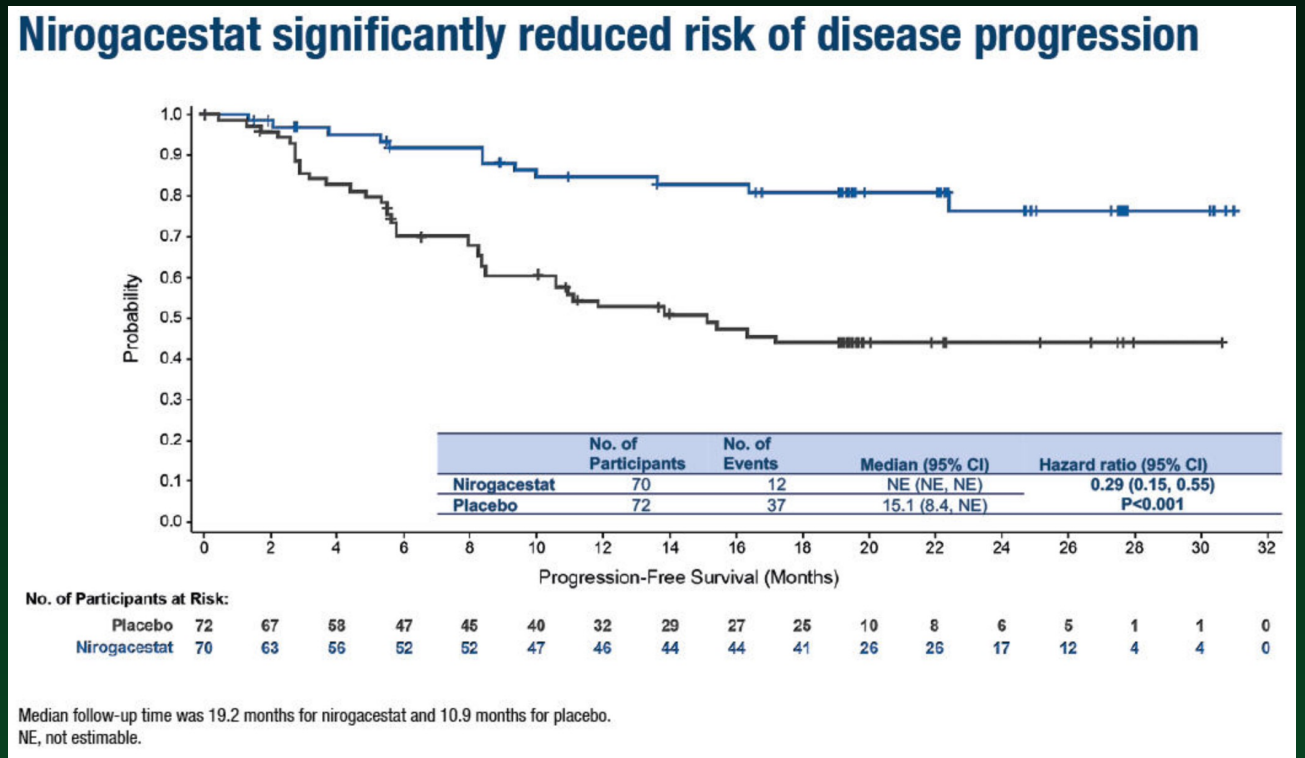
CT



Study baseline | Study cycle 5 day 1 | Study cycle 9 day 1

# Phase 3 Niragacestat vs Placebo
# *Desmoid Tumor*

- First in class, oral gamma secretase inhibitor (GSI)
- 142 adults with progressing desmoid tumours
- **71% reduction** in the risk of progression vs placebo
  - hazard ratio for progression-free survival 0.29, p<0.001
- Significantly superior objective response rate
  - **41%** versus 8%, p<0.001
- More rapid median time to response
  - 5.6 months versus 11.1 months

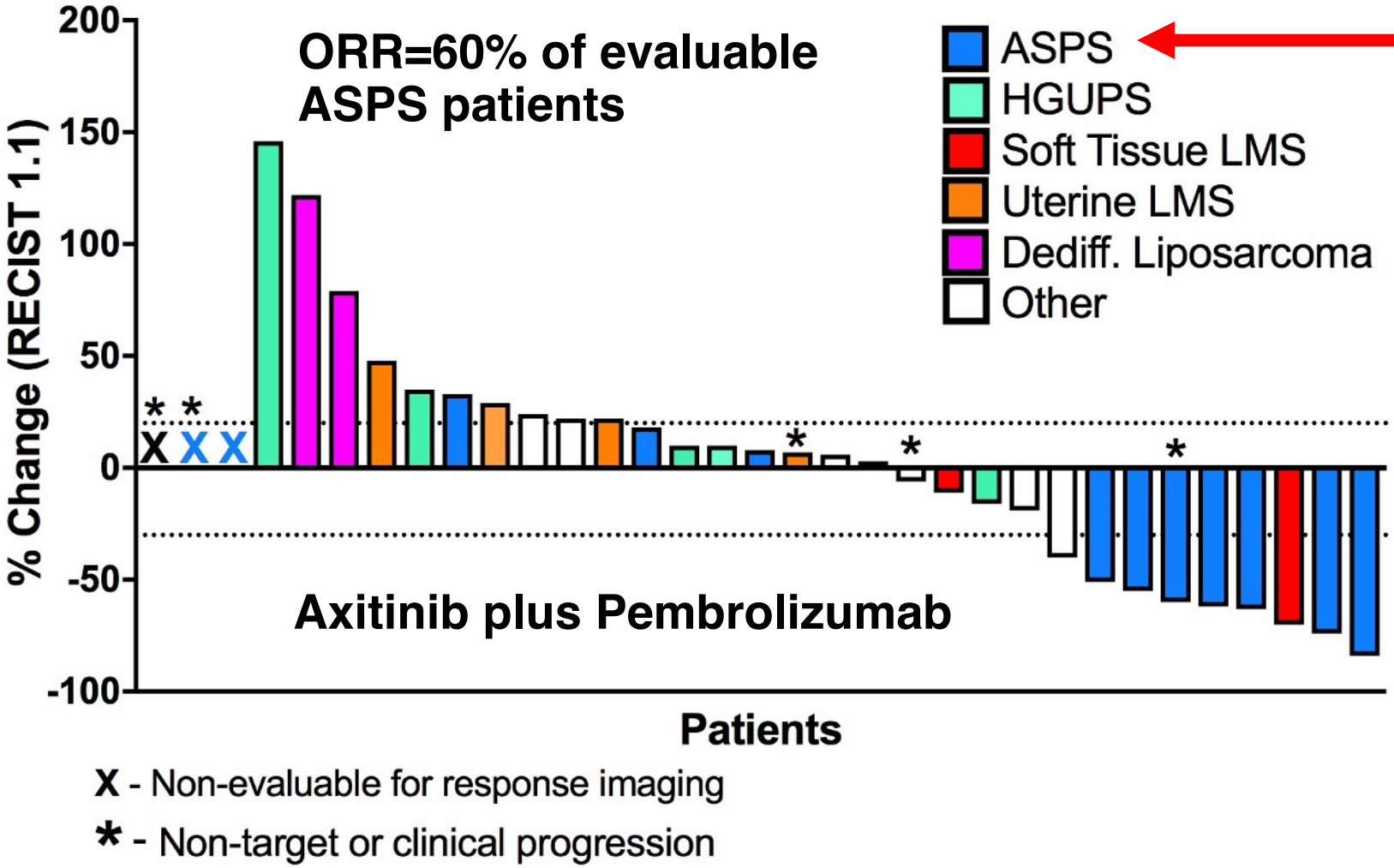



ESMO 2022

# Immunotherapy

# Immune Checkpoint Inhibitors in Angiosarcoma

IN PURSUIT OF *YOUR CURE.*™

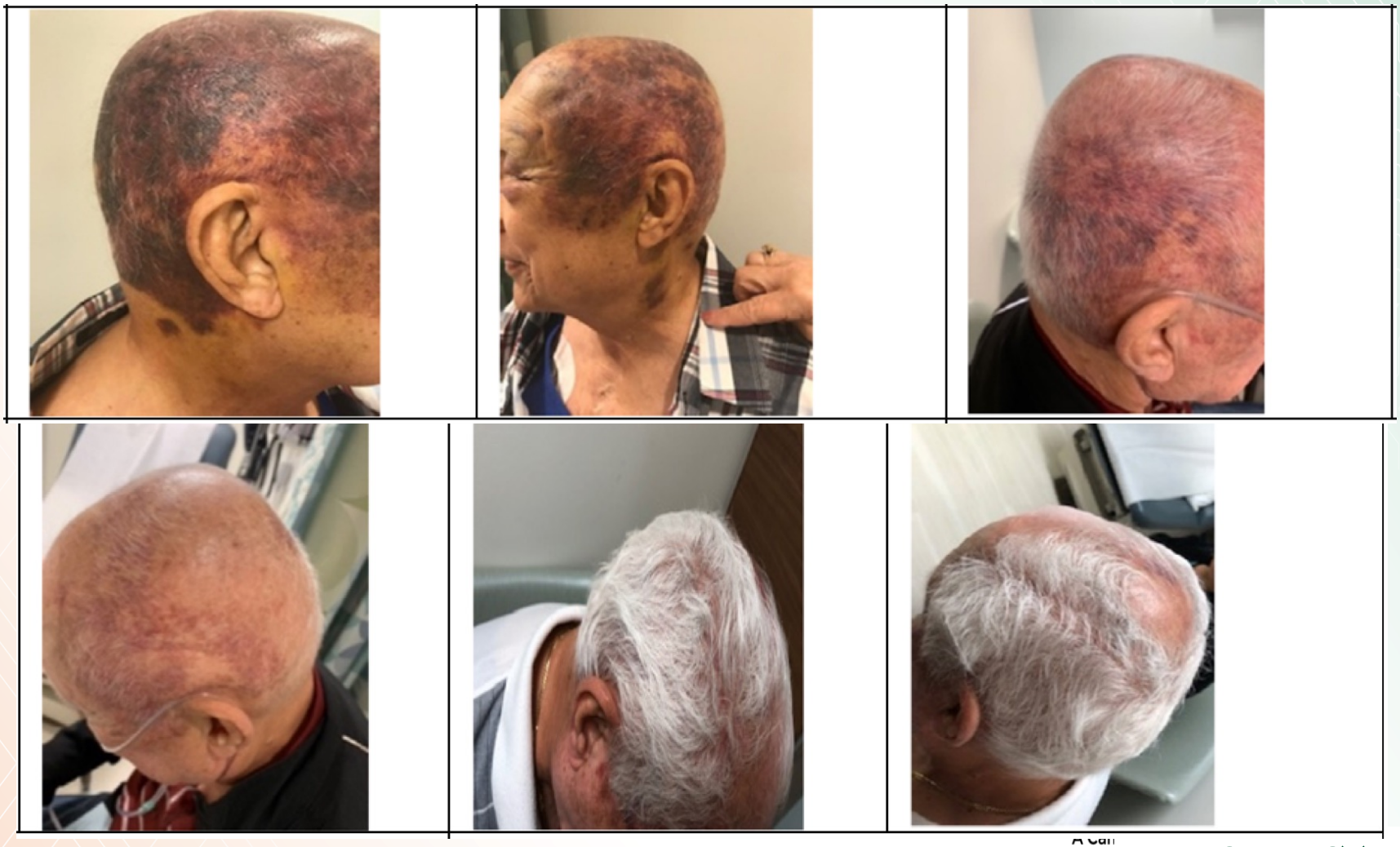



Wilky,…. Trent. Lancet Oncol. 2019 Jun;20(6):837-848. doi: 10.1016/S1470-2045(19)30153-6

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# TKI plus Immune Checkpoint Inhibitors in Alveolar Soft-part Sarcoma (ASPS)

IN PURSUIT OF *YOUR CURE.*™



Florou V, Rosenberg AE, Wieder E, Trent, et al Angiosarcoma patients treated with immune checkpoint inhibitors. Journal for ImmunoTherapy of Cancer 2019;7:213.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Conclusions

- “Sarcoma” is a collection of 175 unique types of primary bone or soft-tissue cancers
- Diagnosis by an experienced Sarcoma pathologists is recommended
- Dose intense, cytoxic chemotherapy is standard front-line therapy for treatment of primary and most metastatic sarcoma types
- Precision medicine approaches are critical in select sarcoma types

# *Sarcoma Team*

- **Medical Oncology**
  - Jon Trent
  - Gina D'Amato
  - Emily Jonczak
  - Aditi Dhir (Ped)
- **Pathology**
  - Andrew Rosenberg
  - Elizabeth Montgomery
  - Daniel Cassidy
  - Jay-Lou Velez Torres
- **Radiology**
  - Ty Subhawong
  - Francesco Alessandrino
- **Nurse Practitioner**
  - Morgan Smith
  - Solange Sierra
  - Yolanda Roper
- **Nursing**
  - Eryka Lacayo
  - Vilma Sanchez
  - Lila Wong
  - Amanda Martin
- **Social Work**
  - Marlene Morales
  - Adriana Alvaraez (AYA)

- **Orthopedic Oncology**
  - Fran Hornicek
  - Tom Temple
  - Sheila Conway
  - Frank Eismont
  - Juan Pretell
  - Mo Al Maaieh
- **Surgical Oncology**
  - Nipun Merchant
  - Alan Livingstone
  - Neha Goel
  - Dido Franceschi
- **Radiation Therapy**
  - Raphael Yechieli
  - Aaron Wolfson
  - Laura Freedman
- **Head & Neck Surgery**
  - Zoukaa Sargi
  - Frank Civantos
- **Thoracic Surgery**
  - Dao Nguyen
  - Nestor Villamizar

- **Interventional Radiology**
  - **Shree Venkat**
  - **Prasoon Mohan**
- **Gynecologic Oncology**
  - **Matt Schlumbrecht**
  - **Marilyn Huang**
- **Clinical Research**
  - **Josefina Sanchez**
  - **Melissa Serna**
  - **Mirna Gonzalez**
  - **Karyms Luna**
- **Lab Research**
  - **Zhefeng Duan, PhD**
  - **Luyuan Li, PhD**
  - **Karina Galoian**
  - **Josie Eid, PhD**
- **Fellows/Residents**
  - **Andrea Espejo**
  - **Priscella Coelho**
  - **Phillipos Costa**
  - **Caroline Hana**
  - **Briana Valdes**
  - **Steven Bialick**
  - **Anthony Skyrd**

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

# Soft-tissue Sarcomas

## *Diagnosis and Management*


**Jon Trent, MD, PhD**

**Professor of Medicine**
**Director, Bone and Soft-tissue Sarcoma**
**Associate Director, Clinical Research**
**The University of Miami,**
**Sylvester Comprehensive Cancer Center**
**jtrent@med.miami.edu**
**@JTrentMDPhD**


SYLVESTER
COMPREHENSIVE CANCER CENTER

UNIVERSITY OF MIAMI HEALTH SYSTEM